Risk-Based Approach and CBER Compliance

Current GMPs for the Pharmaceutical Industry
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James S. Cohen, J.D.

Acting Director, Office of Compliance and Biologics Quality

Center for Biologics Evaluation and Research

Food and Drug Administration

Risk-Based Approach and CBER Compliance

- Biologics: Unique Attributes and Risk Issues
- Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach
- Systems-Based Inspections
- FDA's Counterfeit Drug Initiative

Biologics: Unique Attributes and Risk Issues

- Biologic sources (human/animal communicable diseases)
- Multiple mechanisms of action
- Predictors of toxicity often not established
- Complex manufacturing processes
- Most biologics are complex mixtures that tend to be heat sensitive and open to microbial contamination. Aseptic principles are used during manufacturing, unlike most conventional drugs

Unique Attributes and Risk Issues
continued

- Broad range of affected individuals
  - Healthy to elective surgery to severely ill
- Uncertainty
  - For example, emerging infectious disease threats
  - Cutting-edge technology: less experience, more interest
- Products often needed for public health; multiple partners (government & industry)
- Often no substitute product

Unique Attributes and Risk Issues
continued

- Supply and availability as public health issue and factor in risk/benefit assessments
- Acute problems with limited information on product
- High public interest
- Perceived-real needs for immediate action

Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach

- FDA initiative announced in August 2002
- Two-year + program
- Applies to pharmaceuticals, including biological human drugs and veterinary drugs (excludes blood/plasma)
- Steering Committee comprised of CBER, CDER, CVM, CDRH*, CFSAN*, ORA, and the Office of the Commissioner

Objectives

- Encourage early adoption of new technological advances by pharmaceutical industry
- Facilitate industry application of modern quality management techniques, including quality systems approaches, to all aspects of pharmaceutical production and quality assurance

Objectives
continued

- Encourage implementation of risk-based approaches that focus both industry and Agency attention on critical areas
- Ensure regulatory review and inspection policies are based on state-of-the-art pharmaceutical science

Objectives
continued

- Enhance consistency and coordination of FDA drug quality programs, in part, by integrating enhanced quality systems approaches into the Agency's business processes and regulatory policies concerning review and inspection activities

Compliance-Related Accomplishments

To date, accomplishments include:

- 21 CFR Part 11 – Electronic Records Requirements (Final Guidance - posted 9/5/03)
  - Withdraws earlier guidance
  - Clarifies scope and application of regulation
- Implementation of a Technical Dispute Resolution Process for CGMP Disputes (Draft Guidance - posted 9/3/03)
  - Domestic pilot study began 1/1/04
  - Intended to promote open, prompt discussion and resolution of scientific/technical questions and issues raised during routine biennial inspections

Compliance-Related Accomplishments
continued

- Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice (Draft Guidance – posted 9/5/03)
  - Updates, clarifies, and replaces 1987 "Industry Guideline on Sterile Drug Products Produced by Aseptic Processing"
- Comparability Protocols – Protein Drug Products and Biological Products – Chemistry, Manufacturing, and Controls Information (Draft Guidance – posted 9/5/03)
  - Guidance for use for changes in CMC products in approved marketing applications

Compliance-Related Accomplishments
continued

- Center review of all proposed drug CGMP Warning Letters started March 1, 2003
  - CBER had previously implemented review of all biological drug and device Warning Letters
- Language added to Form FDA 483
  - Clarifies that 483 items are inspectional observations and do not represent final FDA compliance determination
  - Notes that firm may discuss disagreement regarding an observation or a plan for corrective action with FDA representatives

Compliance-Related Accomplishments
continued

- Scientific workshop held April 22-24, 2003, in Washington, DC
- Developing risk-based approach for choosing sites for inspections (CDER)
  - CBER already meets statutory obligations for inspecting all licensed facilities

Compliance-Related Accomplishments
continued

- Review of Team Biologics operations
- Pharmaceutical Inspectorate program established by ORA and CDER on 8/22/03
  - Highly trained individuals
  - Increased use of product specialists
  - Similar to existing Team Biologics and CBER biologics inspection practice (e.g., product specialists on inspections)

Quality Management Systems

- Design of integrated Agency-wide, risk-based quality management system
- Three working groups established
  - Framework
  - Guidance
  - Harmonization

Quality Systems Framework

- Development of framework that enhances and integrates Agency's existing quality systems
- To be implemented in Centers and field to ensure consistency of reviews and inspections
- Common vocabulary and component description
- Framework submitted to Steering Committee and adopted December 2003

Quality System Guidance Development

- Development of new educational guidance documents to encourage use of quality system principles
- First guidance expected to be released August 2004

CGMP Harmonization Analysis

- Analyzing internal and external GMP requirements
- Review of regulations
  - 21 CFR 210 and 211
  - European Union CGMPs
  - PIC/S
  - Agency-wide CGMP regulations
- Differences noted will contribute to assessment of whether or not to revise 21 CFR 210 and 211
- Interim report presented to Steering Committee in December 2003
- Final report expected in May 2004

CBER's Existing CGMP Innovations Support FDA's Initiative

- Core Team of Investigators with specialized training in biologic drugs and devices
- Product specialists on-site or available during inspections
- All Warning Letters for biological drugs and devices reviewed by CBER
- Risk-based work planning
  - Products covered biennially
  - Most considered high-risk

Counterfeiting/Tampering

- The Problem and the Risks
- FDA's Counterfeit Drug Initiative
- CBER Experience/Examples

The Problem and the Risks

- Substantial increase in counterfeiting nationally and internationally in recent years
  - Better technology available to counterfeiters
  - Increasing sophistication of counterfeiting operations
  - Online sale of prescription drugs
  - Increased international commerce
  - Weak spots in domestic wholesale drug distribution chain

The Problem and the Risks
continued

- Subpotent or superpotent ingredients
- No active ingredients
- Ineffective treatments
- Infections or other potential detrimental health effects

FDA's Counterfeit Drug Initiative

- Commissioner priority
- Announced July 16, 2003
- Designed to:
  - Better identify the risks and threats from counterfeit drugs
  - Establish a public and private coalition to fight drug counterfeiting and distribution
  - Develop new tools to aid in identifying, deterring, and combating counterfeiting
- CBER representative on Commissioner's Task Force

FDA's Counterfeit Drug Initiative
continued

- Internal FDA task force is working to:
  - Develop strategic plan to decrease risk of counterfeits entering U.S. marketplace
  - Strengthen FDA's collaborative relationships with other Federal agencies
  - Identify mechanisms for strengthening nation's protections against counterfeiting
  - Assess the extent to which new technologies can help assure authenticity of products

FDA's Counterfeit Drug Initiative
continued

- Specifically, FDA task force is exploring:
  - Technology (e.g., track and trace, RFID, overt and covert protections)
  - Border study
  - Alert system
  - Strengthening distribution system
  - Engaging private sector stakeholders
  - Engaging other Government agencies
  - Public education
  - Higher penalties
- Industry is fully engaged in the anti-counterfeiting strategy and effort

FDA's Counterfeit Drug Initiative
continued

- Interim Report issued October 2, 2003 – detailed discussion of preliminary options
- Public meeting October 15, 2003
- Final Report expected by late February or in March 2004

CBER Experience/Examples

- CBER performs dual role
  - Safety
  - Availability
- Has established procedures for promptly responding to and addressing potential and actual counterfeiting events
- Collaboration with FDA's Office of Criminal Investigations (OCI)
  - Aggressive enforcement strategy
- CBER's response serves as model for addressing counterfeiting events

CBER Experience/Examples

continued

- First priority is to provide consumers timely and relevant information relating to safety and quality
- Related priorities are to investigate scope of event, assure removal from market, and investigate counterfeiters
- Work closely with manufacturers in getting public health message out and containing counterfeit event
- Sources of information include surveillance, consumers, industry, other FDA components, and other Government agencies

Counterfeiting of Biologics

Recent Examples

- Neupogen®
  - May 2001 - vials containing clear liquid but no active ingredient
- Epogen®
  - May 2002 – vials containing clear liquid but active ingredient 20 times lower than expected
- Procrit®
  - April 2003 – Expired vials containing clear liquid but active ingredient 20 times lower than expected
  - March 2003 – Vials containing no active ingredient but clear liquid contaminated with bacteria
  - June 2002 - Vials containing clear liquid but active ingredient 20 times lower than expected

Systems-Based Inspections

- Traditional Inspection Approach
- Systems-Based Inspections
  - Drug Manufacturing Inspections Program 7356.002
  - http://www.fda.gov/cder/dmpq/compliance_guide.htm
- Further development of CBER's risk-based compliance strategy
  - Blood Compliance Program (September 1, 2003)

"Traditional" Inspections

Team Biologics

- Audit approach
- Comprehensive biennial inspection

➢ Pros
  - – Very thorough
  - – High level of assurance of identifying problems

➢ Cons
  - – Resource intensive
  - – Often lengthy
  - – Broadly focused

Elements of Systems-Based Inspections

- Risk management
- Focus on critical systems
- Provides method to determine level of inspectional coverage and resources appropriate for each inspection

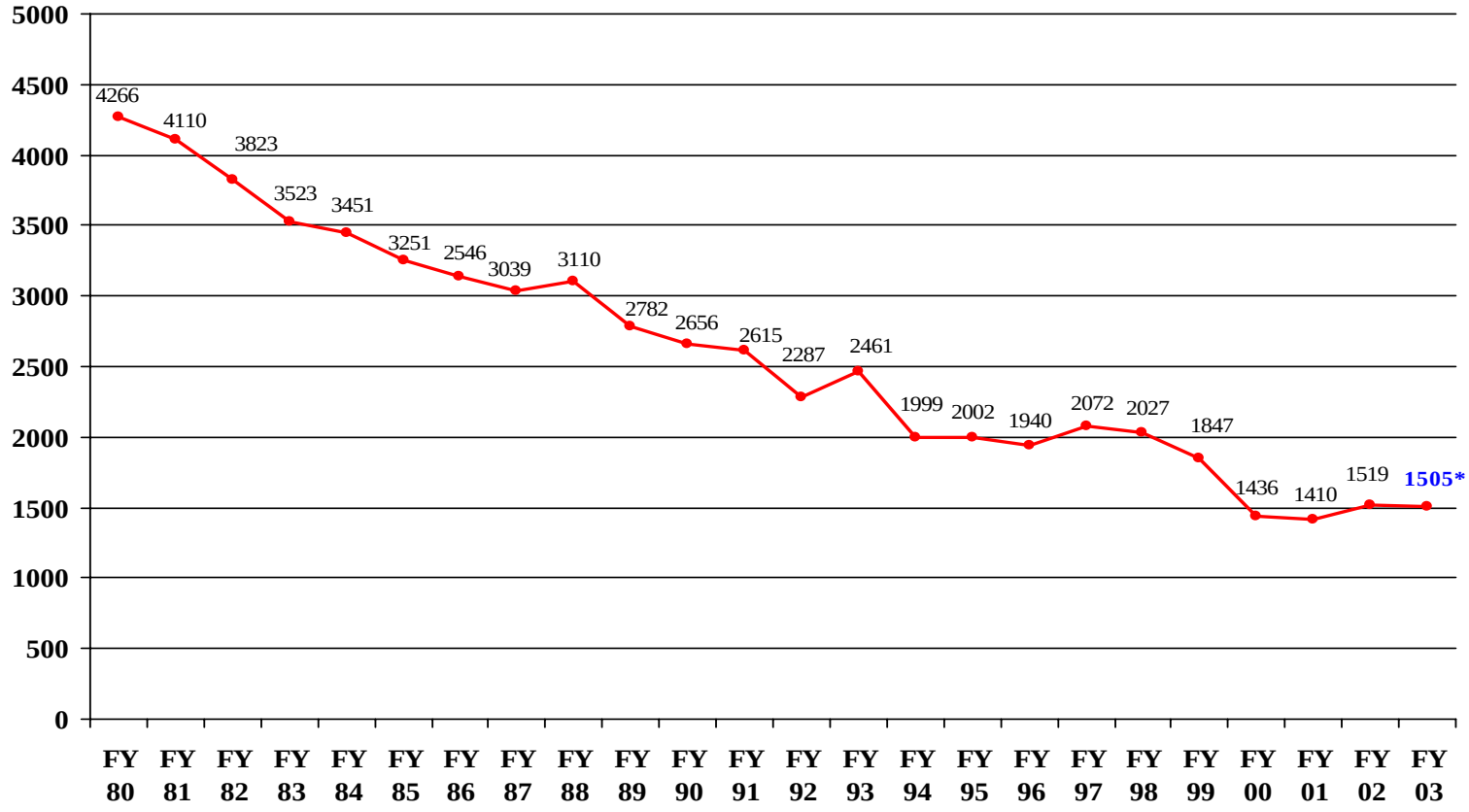
Why Systems-Based Inspections?

- Ties in with Agency's risk-based initiative
- Commissioner's Strategic Plan
  - Efficient risk management
  - Improving healthcare through better information
  - Improving patient and consumer safety
  - Protecting America from terrorism
  - Smarter regulation through a stronger workforce
- Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach

Why Systems-Based Inspections?
continued

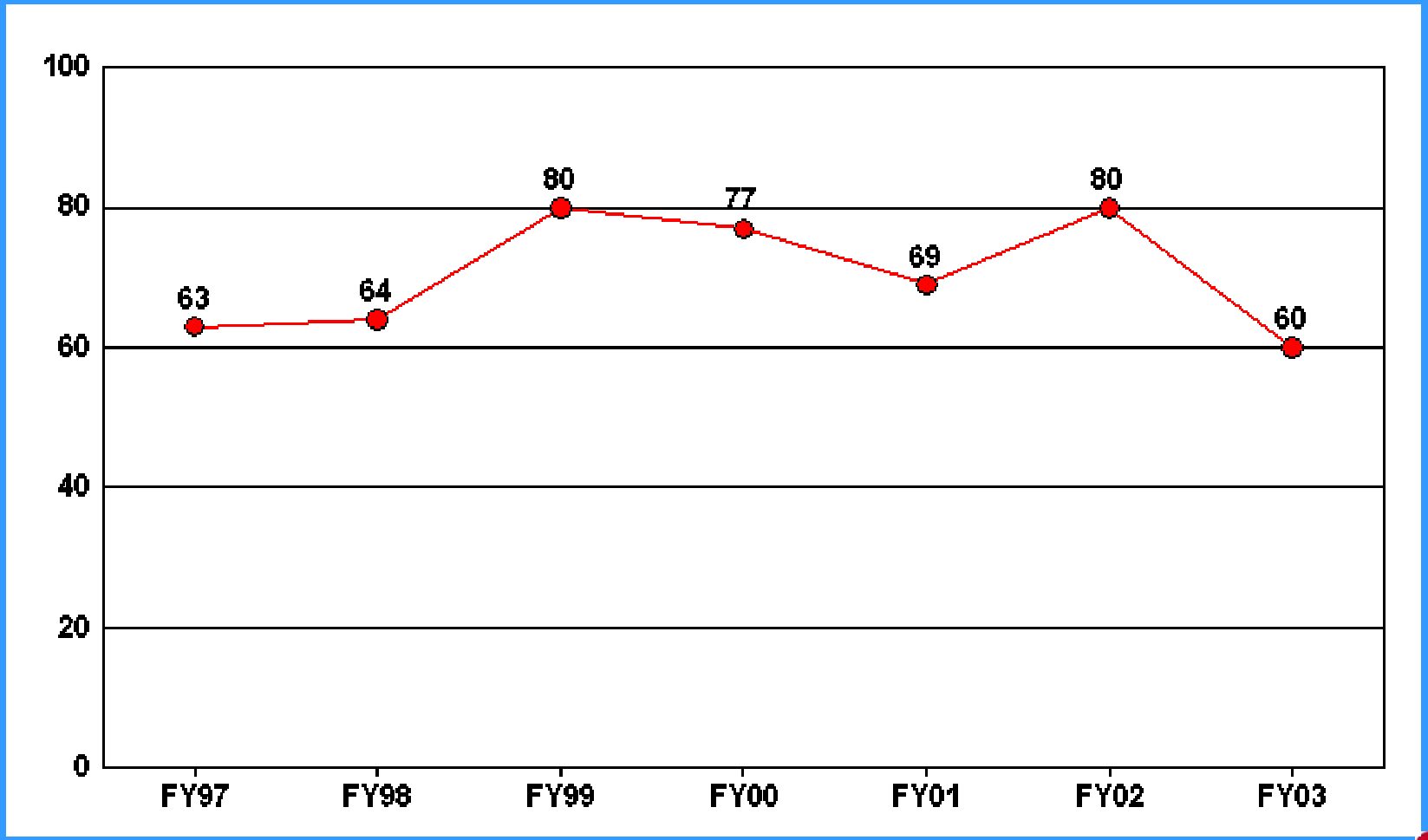
- More Focused Inspections
  - Identify and train Investigators on:
    - Critical systems
    - Critical issues within the systems
    - Specific technical training

Domestic CGMP Drug Inspections



* planned

CGMP Biologic Inspections



Why Systems-Based Inspections?
continued

- Best Use of Resources
  - Reduce inspection length
  - In-depth only where warranted
  - Use resources to conduct more inspections, develop guidance, etc.
  - Optimize level of effort necessary to determine compliance

Drug/Blood Examples

- Drug Manufacturing Inspections Program
  - CDER
- Inspection of Licensed and Unlicensed Blood Banks, Brokers, Reference Laboratories, and Contractors
  - CBER

Systems

Drug/Blood Examples

DRUG

- Quality
- Laboratory control
- Materials
- Production
- Facilities and equipment
- Packaging and labeling

BLOOD

- Quality Assurance
- Product Testing
- Donor Eligibility
- Production and Processing
- Quarantine/Inventory Management

Critical Areas

Drug/Blood Examples

- Inspection will include in-depth audit of critical areas in each system (drug and blood):
  - Standard Operating Procedures
  - Personnel/Training
  - Facilities
  - Equipment Calibration and Maintenance
  - Records

Inspection Options

Drug/Blood Examples

DRUG

- Full inspection option
  - At least four systems
  - Must include Quality system
- Abbreviated inspection option
  - At least two systems
  - Must include Quality system

BLOOD

- Level I inspection
  - All five systems
- Level II inspection
  - Three systems
  - Always includes Quality Assurance and Donor Eligibility

Selection of Systems

Drug/Blood Examples

- Selection of the systems covered is based on:
  - Firm's specific operation
  - History of previous coverage
  - History of compliance
  - Other priorities determined by District Office
  - Assessment of reports – e.g., BPDRs, recalls, etc. (blood)

CBER Compliance Plans

- Additional CBER initiatives
  - Internal Workgroup consisting of experts from pre-approval, post-approval, and enforcement areas
  - Working on plan to revise CBER compliance programs to further develop risk/systems-based inspection approach (e.g., source plasma, tissue, fractionators, vaccines, and allergenics)
  - Next revision – source plasma compliance program

Information and Contacts

- www.fda.gov/cber
- Email CBER
  - Manufacturers
    - matt@cber.fda.gov
  - Consumers, health care professionals
    - octma@cber.fda.gov